Scand J Work Environ Health 2001;27(1):14—20

Reconciling animal and human data in a cancer risk assessment of acrylonitrile

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Schulz MR, Hertz-Picciotto I, Todd L, Ball LM. Reconciling animal and human data in a cancer risk assessment of acrylonitrile *Scand J Work Environ Health* 2001;27(1):14—20.

Objectives Bioassays of rats exposed to acrylonitrile have consistently detected an elevated incidence of central nervous system (CNS) cancer. In contrast, epidemiologic studies have not found a statistically stable increase in CNS cancer mortality. The purpose of this paper is to examine whether or not CNS cancers predicted from the most appropriate inhalation bioassay in rats are consistent with CNS cancers observed in 3 recent, large epidemiologic studies.

Methods A linearized multistage model was fit to dose-response data from a rat inhalation bioassay to estimate carcinogenic potency. This potency was applied to epidemiologic studies of acrylonitrile-exposed workers. After adjustment for less than complete lifetime follow-up in the epidemiologic studies, consistency was examined between CNS cancers predicted by the model fit to the animal data for the exposure levels and sample sizes of the epidemiologicy studies and the CNS cancers observed in the epidemiologic studies.

Results The model predicted totals of 17.7, 3.6, and 7.6 CNS cancer deaths for the studies. These predictions were not far from the observed CNS cancer deaths (12, 6, and 6) and were well within their 95% confidence intervals of 6.9—22.3, 2.2—13.1, and 2.2—13.1, respectively.

Conclusions The CNS cancer potency estimated from the best available inhalation bioassay was consistent with the observed deaths in the epidemiologic studies as long as continuous lifetime exposure was chosen as the exposure metric. The lack of observed excess in CNS cancer among the studied workers may have been due to low exposures, insufficient follow-up times, or both.

Key terms bioassays, carcinogenic potency, central nervous system cancer, epidemiologic studies, follow-up time, interspecies comparison.

Acrylonitrile, a group 2B carcinogen as rated by the International Agency for Research on Cancer (IARC) (1), is widely used in the production of acrylic fibers, resins, and nitrile elastomers and also as an intermediate in the production of adiponitrile and acrylamide (2). In the mid-1970s, approximately 125 000 workers in the United States (US) were potentially exposed to acrylonitrile during its production and use (3). Since then, its worldwide consumption has increased (2). The production of acrylonitrile and acrylic fibers has been moving to newly industrialized nations, where the regulation and monitoring of exposures may not be as stringent (4).

Epidemiologic studies of acrylonitrile-exposed workers and bioassays of acrylonitrile-exposed animals are apparently contradictory. Whether rats are exposed to acrylonitrile by gavage, drinking water, or inhalation, bioassays consistently show elevated incidences of cancer in the mammary gland, Zymbal gland, and particularly the central nervous system (CNS) (5). In contrast, none of the epidemiologic studies, which were recently reviewed by Collins & Aquavella (6), found a large or statistically stable increase in CNS cancer incidence or mortality among exposed workers. CNS cancer is difficult to study in human populations because it is relatively rare. The annual mortality rate is currently around 5 per 100 000 (7). Overall survival averages only 1—3 years (8).

In 1993, Ward & Starr (9) concluded that the occupational epidemiologic studies had sufficient statistical power to detect the CNS cancer risk predicted from bioassays in which acrylonitrile was administered orally, and their analysis was updated in 1999 by Collins & Strother (10), who concluded likewise that the most recent epidemiologic studies were not consistent with the

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risk from acrylonitrile exposure predicted from animal data. Against this background, the American Conference of Government Industrial Hygienists (ACGIH) recently changed their classification of acrylonitrile from an A2 suspected human carcinogen to an A3 confirmed animal carcinogen with unknown relevance to humans (11)

Because the route of exposure may be a key determinant of potency and because workers appear to be predominantly exposed by inhalation (1), this paper, in contrast to the analysis of Ward & Starr (9) or Collins & Strother (10), compares predictions from the inhalation bioassay in rats with CNS cancers observed in the 3 recent, large epidemiologic studies that included quantitative exposure levels for acrylonitrile-exposed workers. For this purpose, we estimated the CNS cancer potency of acrylonitrile in rats on the basis of an inhalation bioassay (Quast J, Schuetz D, Balmer M, Gushow T, Park C, McKenna M. A two-year toxicity and oncogenicity study with acrylonitrile following inhalation exposure in rats. Prepared by the Toxicology Research Laboratory, Health and Environmental Sciences, Dow Chemical, Midland, Michigan, United States, for the Chemical Manufacturing Association in 1980, unpublished observations) and, unlike Ward & Starr (9) or Collins & Strother (10), applied the potency to the actual observed follow-up time in the epidemiologic studies. By calculating the number of deaths predicted for the actual follow-up time of the workers and comparing them with the observed number of deaths and their confidence intervals, we explored the role of dose and follow-up time in explaining the apparently contradictory results for CNS cancer and exposure to acrylonitrile. This approach has been used previously to evaluate consistency between animal and human data (12, 13, 14).

Subjects and methods

Animal studies

We focused on inhalation bioassays in animals because workers are exposed to acrylonitrile primarily by this route. Quast et al exposed Sprague-Dawley (Spartan strain) rats to acrylonitrile concentrations of 20 ppm or 80 ppm, 6 hours a day, 5 days a week for 2 years, and reported a statistically significant increased incidence of brain or spinal cord tumors (benign and malignant) for both the males and females. No CNS tumors were found in the control rats, while CNS tumors were found in 4 of 99 male rats exposed to 20 ppm and in 22 of 99 male rats exposed to 80 ppm. Of the other 2 inhalation bioassays (15, 16), one (15) has limited value for estimating cancer risk because the exposure and follow-up were subchronic, and the other (16) began dosing the rats while they were still in utero, an exposure scenario unlikely among workers. We therefore selected the Quast et al, inhalation bioassay with its standard exposure scenario.

Epidemiologic studies

Collins & Strother (10) identified 11 unique follow-up studies and 1 case-referent study that examined the association between acrylonitrile exposure and CNS cancer. Using meta-analysis techniques, they calculated a summary relative risk of 1.1 [95% confidence interval (95% CI) 0.8—1.5]. However, only 3 epidemiologic studies — a National Cancer Institute (NCI) multiplant study in the United States (17), a Dutch multiplant study (18), and a study of 2 DuPont plants in the southeastern part of the United States (19) — relate CNS mortality to quantitative exposure levels. The summary relative risk for these 3 studies was 1.0 (95 CI 0.6—1.5) (6). None of these studies demonstrated a strong statistically stable elevation in risk or a positive dose-response relationship between cumulative exposure to acrylonitrile and the risk of CNS cancer mortality. Nevertheless, these 3 cohorts were large, had an extended follow-up time, and quantified exposure estimates for individual cohort members. Considered on the basis of the framework for using epidemiologic data in risk assessment developed by Hertz-Picciotto, these are all category 2 studies (12). They therefore can be used to evaluate the plausibility of the quantitative risk estimated from the animal dose-response data.

Estimating excess lifetime risk

The linearized multistage model was fit to the Quast et al dose-response data using the software package Global 86 (20). The model assumes a linear nonthreshold dose-response relationship and takes the following form:

$$P(d_{HEC}) = 1 - \exp[-q_1 d_{HEC} - q_2 (d_{HEC})^2],$$

where $P(d_{HEC})$ is the lifetime risk of cancer at dose d_{HEC}, d_{HEC} is the human equivalent concentration, q_1 is the estimated low dose potency (obtained by maximizing the likelihood given the rat dose-response data), and q_2 is the coefficient for the quadratic dose term (which does not materially affect the risk at low doses).

The cancer guidelines proposed by the US Environmental Protection Agency (EPA) (21) advocate using a biologically based model to translate experimental exposure concentrations (d_A) to d_{HEC}; however, no such model is available for acrylonitrile at this time. We therefore followed the EPA default recommendation (22, 23) summarized in the following equation:

$$d_{HEC} = \text{equivalent continuous lifetime exposure } (\lambda_A/\lambda_H),$$

where λ_A/λ_H is the ratio of the blood-to-gas air partition coefficient for acrylonitrile in rats to the same

coefficient in humans. Following the example of Felter & Dollarhide (24), we assumed λ_A/λ_H to be unity. Finally, the predicted excess lifetime risk of CNS cancer in humans was calculated by substituting the equivalent continuous lifetime exposure in the human epidemiology study (d_H), for d_{HEC} in equation 1 after q_1 and q_2 were estimated from the modeling of the rat data. For comparison, we also made calculations using (i) cumulative exposure for the species conversion, (ii) the maximum likelihood potency estimated by Felter & Dollarhide (24), and (iii) the maximum likelihood potency estimated by Ward & Starr (11) from drinking water bioassays.

Predicted cancers of the central nervous system in the human cohorts

The predicted excess lifetime risks were used to characterize the risk of the 3 cohorts of acrylonitrile-exposed workers. Because most of the workers were not followed for their entire lifetime, we adjusted the resulting predicted CNS deaths for the actual follow-up time. These adjusted predictions for excess mortality were added to the expected (background) CNS cancer deaths. The predicted total was then compared with the observed CNS cancer deaths and their confidence intervals. Similarly, to take account of the uncertainty in the estimated potency, the upper confidence limit of the total predicted deaths was compared with the observed number of deaths. An epidemiologic study was judged consistent, or at least not inconsistent, with the animal bioassay if the 95% confidence interval of the observed deaths in the cohort surrounded the number of deaths predicted by the extrapolation.

Proportion of lifetime risk accumulated by epidemiologic cohorts

The proportion of lifetime risk accumulated by a cohort was estimated as follows: (i) the expected number of CNS cancer deaths in each cohort was divided by the number of workers to estimate average background risk, (ii) the average cumulative "lifetime" risk of CNS cancer death by 74 years of age for males in the United States was calculated using a lifetable constructed from US male, 1990—1994, age-specific all-cause (25) and brain cancer death rates (26) [For the Dutch cohort, Dutch 1990—1994 age-specific rates were used (personal communication, Jan Hoogenboezem, The Netherlands Central Bureau of Statistics], (iii) the ratio of step i to step ii estimates the proportion of lifetime risk accumulated by a cohort. Finally, the predicted excess CNS cancer deaths obtained from the animal-based potency were multiplied by the estimated proportion of lifetime risk accumulated by the cohort. This last step accounted for the animal potency being based on a full (rat) lifetime, while workers were observed for partial lifetimes. The adverse consequences of failing to adjust for different study designs and follow-up times in animal bioassays and epidemiologic studies when the results of the 2 study types are compared have been highlighted previously (27).

Summary of three human cohorts

We compared the total of the predicted CNS cancer deaths from the NCI, Dutch, and DuPont cohorts to the 95% confidence interval of the observed deaths derived from the Collins & Strother (10) summary relative risk for the 3 studies. The summary was judged consistent, or at least not inconsistent, with the animal bioassay if the 95% confidence interval of the observed deaths surrounded the deaths predicted by the extrapolation in the summary.

Results

Exposure estimates

Table 1 shows the conversion of the intermittent bioassay exposure rates and the intermittent exposure rates in the epidemiologic studies to equivalent continuous lifetime exposure rates. As is frequently the case, the rats in the lowest dosed group in the Quast et al study were exposed to a substantially greater equivalent continuous lifetime exposure rate than were the most highly exposed workers. For example, the equivalent

Table 1. Summary of the inhalation bioassay and epidemiologic studies with quantitative exposure estimates.

Study	Daily exposure (ppm)	Exposure time (years)	Cumulative exposure (ppm-years)	Continuous lifetime exposure (ppm)
Quast et al, unpublished study 1980 (rats)	20	2	40	3.57[a]
	80	2	160	14.37[a]
NCI, Blair et al 1998 (17) (humans)	..	..	4.026[b]	0.0118[c]
Dutch, Swaen et al 1998 (18) (humans)	..	..	7.31[d]	0.0214[c]
DuPont, Wood et al 1998 (19) (humans)	..	..	57.67[e]	0.168[c]

[a] Cumulative exposure × (5/7 days exposed) × (6/24 hours exposed) / (2-year average lifetime).
[b] Mean (Blair, 1998 personal communication to Mark Schulz).
[c] Cumulative exposure × (240/365 days exposed) × (8/24 hours exposed) / (75 year average lifetime).
[d] Mean (Swaen, 2000 personal communication to Mark Schulz).
[e] Mean as reported in Wood et al (19).

continuous lifetime exposure of the DuPont cohort was 0.168 ppm. In contrast, the continuous lifetime exposure rate of the rats was 3.57 ppm.

Predicted mortality

Table 2 shows the adjustment factors for the average portion of lifetime risk accumulated for each of the 3 occupational cohorts. These factors ranged from 0.27 to 0.55. The estimated acrylonitrile potency for CNS cancer based on the Quast et al rat data was 0.00954 per ppm. The 95% upper confidence limit of the potency was 0.0213 per ppm. When the estimated potency was applied to the epidemiologic studies, the lifetime predicted excess CNS deaths were 1.90 in the NCI cohort, 0.58 in the Dutch cohort, 4.11 in the DuPont cohort, and 6.59 in the combined cohort (table 3). These values represent the excess CNS cancer deaths predicted to occur if all workers were followed to death or "complete" lifetime. However, when adjusted for the proportion of lifetime risk accumulated in the corresponding epidemiologic studies (table 2), the predicted excess was reduced to 0.51 for the NCI cohort, 0.20 for the Dutch cohort,

Table 2. Proportion of lifetime risk accumulated in selected epidemiologic studies. (CNS = central nervous system)

Study cohort	Number in cohort	Expected number of deaths from CNS cancer	Average cumulative lifetime background risk of deaths from CNS cancer[a]	Proportion of lifetime risk accumulated[b]
NCI [Blair et al (17)]	16 889	17.14	0.00101	0.27
Dutch [Swaen et al (18)]	2 842	3.45	0.00121	0.35[c]
DuPont [Wood et al (19)]	2 559	5.31	0.00208	0.55

[a] Expected number of deaths from CNS cancer / number in cohort.
[b] Average cumulative lifetime background risk of deaths from CNS cancer / 0.0037661, which is the average cumulative lifetime background risk for deaths from CNS cancer by the age of 74 years among males in the United States and was calculated from a lifetable based on 1990—1994 age-specific all-cause (25) and brain-cancer death rates (26) for males in the United States.
[c] Average cumulative lifetime background risk for death from CNS cancer / 0.0037661, which is the average cumulative lifetime background risk for death from CNS cancer by the age of 74 years among Dutch males and was calculated from a lifetable based on 1990—1994 age-specific all-cause and brain-cancer death rates for Dutch males (personal communication from The Netherlands Central Bureau of Statistics, 2000).

Table 3. Comparison of observed CNS cancer deaths with deaths predicted from animal dose-response data. (CNS = central nervous system, 95% CI = 95% confidence interval, MLE = maximum likelihood estimate)

Study cohort	Observed deaths		Potency[a]	Excess lifetime risk[b]	Excess deaths[c]	Adjusted excess deaths[d]	Predicted deaths[e]
	N	95% CI					
NCI [Blair et al (17)]	12	6.9—22.3	0.00954	0.000112	1.90	0.51	17.65
			(0.0213)	(0.000251)	(4.23)	(1.14)	(18.28)
			0.180[f]	0.002117	35.75	9.65	26.79
			0.0178[g]	0.000209	3.54	0.95	18.09
			0.00085[h]	0.00342[i]	57.70	15.58	32.72
Dutch [Swaen et al (18)]	6	2.2—13.1	0.00954	0.0002	0.58	0.20	3.65
			(0.0213)	(0.00045)	(1.29)	(0.45)	(3.90)
			0.180[f]	0.00384	10.91	3.79	7.24
			0.0178[g]	0.00038	1.08	0.37	3.82
			0.00085[h]	0.00619	17.60	6.11	9.56
DuPont [Wood et al (19)]	6	2.2—13.1	0.00954	0.001605	4.11	2.26	7.57
			(0.0213)	(0.003579)	(9.16)	(5.04)	(10.35)
			0.180[f]	0.029865	76.42	42.03	47.34
			0.0178[g]	0.002991	7.65	4.21	9.52
			0.00085[h]	0.04778[i]	122.27	67.25	72.56
All 3 studies combined	24	15.5—38.9	0.00954	..	6.59	2.97	28.87
			(0.0213)	..	(14.68)	(6.63)	(32.53)
			0.180[f]	..	123.08	55.47	81.37
			0.0178[g]	..	12.27	5.53	31.43
			0.00085[h]	..	197.57	88.94	114.84

[a] MLE of the potency, in deaths/ppm, based on fitting the multistage model to the data of Quast et al using continuous lifetime exposure as the exposure metric, the 95% upper confidence limit being given below in parentheses.
[b] 1 – exp(–*qd*), where *q* is the potency and *d* is the continuous lifetime exposure from table 1, the 95% upper confidence limit being given below in parentheses.
[c] Excess lifetime risk × number in cohort, from table 2, the 95% upper confidence limit being given below in parentheses.
[d] Excess deaths × proportion of lifetime risk accumulated, from table 2, the 95% upper confidence limit being given below in parentheses.
[e] Expected deaths from table 2 + adjusted excess deaths, the 95% upper confidence limit being given below in parentheses.
[f] MLE potency (deaths/ppm) estimated from drinking water bioassays by Ward & Starr (11).
[g] MLE potency (deaths/ppm) estimated from Quast et al data by Felter & Dollarhide (24).
[h] MLE potency (deaths/ppm-years) based on fitting multistage model to the data of Quast et al using cumulative exposure as the exposure metric.
[i] *d* is the cumulative exposure from table 1 rather than the continuous lifetime exposure.
[j] Sum of the expected deaths from table 2 + adjusted excess deaths.

2.26 for the DuPont cohort, and 2.97 for the combined cohort (table 3).

Table 3 also shows the total CNS deaths predicted on the basis of summing the expected (background) CNS deaths and the adjusted excess predicted from acrylonitrile exposure. For each cohort and for the cohorts combined, the 95% confidence interval of the observed CNS cancer deaths easily included the total predicted deaths. When the 95% upper confidence limit of the potency was applied to the epidemiologic studies, the predicted deaths were slightly greater but still within the 95% confidence interval of the observed deaths (table 3).

In table 3, we have also shown that the total predicted deaths fell outside the 95% confidence interval of the observed deaths for the NCI cohort, the DuPont cohort, and the combined cohort when the potency based on the drinking-water studies was applied [as was done by Ward & Starr (9) and Collins & Strother (10)] or when the exposure metric was cumulative exposure rather than continuous lifetime exposure rate and thus did not account for differences in the average lifetime of rats and humans.

Discussion

Extrapolation, using the multistage model, from the inhalation bioassay dose-response data to the epidemiologic data resulted in a prediction of CNS cancer death totals that was similar to the number of observed CNS deaths. In addition, these predictions lay within each respective 95% confidence interval for the 3 epidemiologic cohorts studied (table 3). An important element of our analysis was the adjustment of the animal-based risk estimate for the proportion of lifetime risk accumulated in each epidemiologic cohort. This adjustment substantially reduces the predicted excess of CNS cancers due to acrylonitrile exposure, by 73% for the NCI cohort, by 65% for the Dutch cohort, and by 45% for the DuPont cohort (table 2). The reductions are large because the cumulative probability of CNS cancer death increases at a greater than linear rate with age (26). This adjustment is particularly large for the NCI and Dutch cohorts because both cohorts were apparently young at the time they were studied.

Thus we found that neither the Dutch study nor the NCI study was inconsistent with our animal-based risk estimate (table 3). Even the results of the DuPont study with its older cohort and the 3-study summary (10) were not inconsistent with the animal-based risk estimate derived from the inhalation bioassay. In contrast, Collins & Strother (10) concluded that their summary of the NCI, Dutch, and DuPont studies was inconsistent with their animal-based risk estimate, and, earlier, Ward & Starr (9) concluded that a subset of the NCI study (28) was inconsistent with their animal-based risk estimate. Three factors contributed to the higher risks predicted by Collins & Strother (10) and Ward & Starr (9). First, their adjustment for less-than-lifetime follow-up assumed a constant CNS cancer rate across all ages from the start of exposure. Since CNS cancer rates increase at older ages (26), we achieved a more realistic adjustment using the proportion of lifetime risk accumulated. Second, they imputed a higher estimate of average cumulative exposure based on estimates of average daily exposure offered by Santodonato (29) for highly exposed acrylonitrile workers during the historical time period of interest. We based our lower mean cumulative exposure estimates for each cohort on the exposure assessments developed specifically for each cohort. Third, they applied a CNS cancer potency (1.8×10^{-1} per ppm) derived from ingestion bioassays; this potency is 18 times larger than that based on the inhalation bioassay. We relied on the Quast et al rat bioassay that used the same route as that through which workers are exposed to acrylonitrile.

We found that the CNS potency estimated by Ward & Starr (9) and used by Collins & Strother (10) was inconsistent with the results of all but the Dutch cohort (table 3) even when we applied an appropriate partial lifetime risk adjustment and the cohort-specific exposure assessments used throughout our analyses. Recently, Felter & Dollarhide (24) estimated a CNS cancer potency for acrylonitrile. They used the risk assessment guidelines proposed by the EPA in 1996 (21) and estimated a CNS cancer potency (1.78×10^{-2} per ppm) for acrylonitrile that is only slightly higher than ours. As we did, these authors selected the Quast et al inhalation bioassay dose-response data as the basis of their potency, but they excluded rats that died before the 1st relevant tumor was observed. We found that the Felter & Dollarhide CNS cancer potency was not inconsistent with the results of the epidemiologic studies.

Using the 95% upper confidence limit of the potency, we estimated the extra risk from exposure to acrylonitrile for a lifetime of work (8 hours/day, 240 days/year, and 45 years/70 years) at the threshold limit value of 2 ppm (11) of the ACGIH as 6 in 1000. This level is somewhat greater than the 1 in 1000 lifetime risk level that the Occupational Safety and Health Administration hopes to achieve with its permissible exposure levels (30).

As in all risk assessments, we made several assumptions in our analysis. The linear nonthreshold dose-response relationship assumed by our multistage model is a major source of uncertainty in this analysis. The multistage model is biologically plausible and usually provides the most health protective extrapolation to low

doses. As such, it has long been the default choice of the US EPA (5).

Current evidence suggests that acrylonitrile is not directly genotoxic. No DNA adducts of acrylonitrile or its metabolites have been identified in rat brain (31). However, recently, increased levels of 8-oxodeoxyguanosine have been found in rats at doses of acrylonitrile similar to those that produced increases in brain tumors (32), and increased levels of 8-hydroxy-2'deoxyguanosine have been found in acrylonitrile-treated Syrian hamster embryo cells in parallel with a dose-dependent increase in morphologically transformed Syrian hamster embryo cell colonies (33). Both Whysner et al (32) and Zhang et al (33) have suggested a possible role for oxidative DNA damage in this carcinogenic process. Nevertheless, the effects of acrylonitrile that produce 8-oxodeoxyguanosine are not yet understood; the dosimetry evidence is not conclusive either for or against our assumption of low-dose linearity for the carcinogenicity of acrylonitrile.

To extrapolate data on rats to humans, we assumed the ppm concentration of acrylonitrile in rats to be equivalent to the same ppm concentration in humans. This approach is advocated by the US EPA (22) for inhalation bioassays in which the toxic agent is partially soluble in water. The US EPA notes that this assumption is based on limited knowledge (22). However, physiologically based pharmacokinetic models for acrylonitrile which could accurately estimate the effective dose to the tissue of interest are not yet available for humans.

We converted the exposure rates of the rats to human equivalent concentrations according to the method of the US EPA (23). This conversion accounts for the different average life spans of rats (2 years) and humans (70 years) in the industrialized world. The resulting continuous lifetime exposure rates in the Quast et al inhalation study were 30 to 1000 times higher than the corresponding average continuous lifetime exposure rates of the acrylonitrile-exposed cohorts (table 1). Generally, bioassays must use much larger exposure rates than those that occur among human populations in order to achieve sensitivity to detect effects with a modest number of animals (34).

Our estimate of human acrylonitrile potency is sensitive to the exposure metric chosen for the animal to human conversion. The lifetime cumulative exposures in the bioassay and in the epidemiologic studies are more similar in magnitude than the continuous lifetime exposure rates are (table 1). When we replicated our analyses using equivalence by lifetime cumulative exposure rather than by average continuous lifetime exposure rate, we found that the results for the NCI cohort, the DuPont cohort, and the summary of the 3 cohorts were no longer consistent with those of the Quast et al inhalation bioassay (table 3). Use of lifetime cumulative exposure equivalence, as opposed to dose rate equivalence, is known to yield much higher estimates of human risk, as it did in this study (35, 36).

Finally, with regard to policy, our results suggest that the ACGIH should reconsider its recent change in the classification of acrylonitrile from an A2 suspected human carcinogen to an A3 confirmed animal carcinogen with unknown relevance to humans. This study demonstrates that the CNS cancer potency estimated from the best available inhalation bioassay is not inconsistent with the observed mortality in 3 recent large epidemiologic studies of workers exposed to acrylonitrile when continuous lifetime exposure is selected as the exposure metric. The data suggest that a risk of 6/1000 at the current threshold limit value of 2 ppm of the ACGIH is not contradicted by any human study. An A3 classification by the ACGIH would appear to imply some discordance between animal and human data (11), while our results suggest that such a judgment is, at the minimum, premature.

Acknowledgments

This research was supported by EPA cooperative agreement CR822673, grant P42-ES05948 from the National Institute of Environmental Health Sciences (NIEHS), NIEHS training grant 5-T32-ES07018, and NIOSH training grant T42/CCT400423-03.

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Received for publication: 3 April 2000